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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,795	SUPURAN ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/26/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/13/2004; 2/09/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on November 11, 2006 in response to the Restriction Requirement of 10/12/2006 has been entered. Applicant's election, with traverse, of Group VII, claims 67-69, as specifically drawn to a method of imaging tumors and/or metastasis that express CA IX in a patient comprising administering a CA IX-specific inhibitor linked to a imaging agent has been acknowledged. However, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The restriction requirement is therefore deemed to be proper and is made FINAL.

Claims 67-84 are currently pending and under consideration.

Species Election

During a telephone conversation with Leona Lauder on January 22, 2007 a provisional election was made with traverse to prosecute the species of Compound 71. Affirmation of this election must be made by applicant in replying to this Office action. However, upon careful review and reconsideration, the Examiner has withdrawn the election of species.

Information Disclosure Statement

The Information Disclosure Statement filed on 02/09/2004 and 08/13/2004 are acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Claims 70-84 are objected to because of the following informalities: It is noted that, new claims 70-84 encompass diagnosing and/or imaging tumors comprising determining "MN/CA IX" expression. While it appears that "MN/CA IX" and "CA IX" are the same molecules (see specification, page 1), it is suggested that Applicants either amend claims 67-69 to recite "MN/CA IX" or amend claims 70-84 to "CA IX" for consistency purposes.

Claim 68 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, it is unclear how the recitation in claim 68 that "CAIX activated by hypoxic conditions is detected or detected and quantitated" further limits independent claim 67.

Clarification is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 68 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 68 recites the limitation "CA IX activated by hypoxic conditions" in the first line. However, upon careful review of independent claim 67 for which claim 68 depends, there is insufficient antecedent basis for this limitation in the claim. For example, independent claim 67 is drawn to a method of diagnosing cancer in a mammalian subject comprising determining the level of CA IX overexpression and does not appear to recite "activated".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67-72 and 76-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The claims encompass CA IX-specific inhibitors useful for the diagnosis of cancer and/or imaging cancerous tissues. The claims are further drawn to CA IX specific inhibitors which are CA IX specific sulfonamides which are useful for the diagnosis of cancer and/or imaging cancerous tissues. Thus, the claims encompass a genus of molecules defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property. However, the written description in this case only sets forth two sub-genus of CA-IX specific sulfonamides useful for diagnostic purposes and/or imaging tumors, wherein the CA-IX specific sulfonamides are aromatic sulfonamides or heterocyclic sulfonamides.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The specification teaches that CA IX specific inhibitors of the invention include, but are not limited to, organic compounds, preferably aromatic or heterocyclic compounds and still more preferably aromatic sulfonamides or heterocyclic sulfonamides (page 11, lines 22-24). The specification further provides a plethora of aromatic sulfonamides and heterocyclic sulfonamides (page 13 to page 14, pages 63-64 and page 66). Thus, while the specification reasonably conveys a

representative number of CA IX specific aromatic and heterocyclic sulfonamides inhibitors which may be useful for diagnosing a tumor, there is insufficient written description encompassing the claimed genus because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a CA IX specific inhibitor are not set forth in the specification as-filed; and therefore, is not commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Similarly, a CA IX specific inhibitor "useful for diagnosing a tumor" does not distinguish any a particular compound from others having the same activity or function and as such does not satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description;

isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

In the absence of structural characteristics that are shared by members of the genus of a CA IX specific inhibitors; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Claims 67-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing cancer and/or hypoxia in a tissue and in vivo imaging of a tumor and/or hypoxic tissue in a patient comprising administering a labeled antibody which specifically binds CA IX, wherein overexpression of CA IX is indicative of cancer, does not reasonably provide enablement for a method of diagnosing cancer and/or hypoxia in a tissue and in vivo imaging of a tumor and/or hypoxic tissue in a patient comprising administering a CA-IX specific inhibitor selected from compounds 1-91. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of imaging a tumor and/or hypoxic tissue in a patient comprising administering a CA IX specific inhibitor, wherein overexpression of CA IX as compared to a control sample is indicative of a precancerous or cancerous condition. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of diagnosing cancer and/or hypoxia in a tissue and an in vivo method of imaging of a tumor and/or hypoxic tissue in a patient comprising administering a CA IX specific inhibitor and detecting the binding of CA-IX specific inhibitor, wherein overexpression of CA IX as compared to a control is indicative of cancer. The claims are further drawn to CA-IX specific inhibitors selected from a group consisting of compounds 1-91.

Guidance in the specification and Working Examples

The specification teaches that the expression of CA IX is restricted to only few normal tissues, but is tightly associated with tumors, wherein it is also regulated by cell density in vitro and is strongly induced by tumor hypoxia in vitro and in vivo (page 2, lines 10-12). As such, the specification teaches that certain carbonic anhydrase inhibitors which are specific for CA-IX would be useful for diagnostic/prognostic methods including imaging methods, such as scintigraphy and for gene therapy (page 9, lines 23-31). With regards to the CA-IX specific inhibitors, the specification teaches the generation of 91 heterocyclic and aromatic sulfonamides and screening assays showing the inhibition of CA-IX protein (CA-IX protein also referred to as MN protein) (page 42 and 47, line 27 to page 50, line 25). Moreover, the specification teaches a comparison of CA-IX specific inhibitor, e.g., compounds 71-91, with other CA isozymes, wherein all compounds appeared to act as inhibitors of CA isozymes , I, II, and IV, as well as the claimed CA IX (page 50, line 26 to page 52, line 30). Thus, while the specification clearly teaches that the instant compounds are successful inhibitors of the claimed CA IX isozyme, as well as CA isozymes, I, II and IV, the specification does not appear to provide a nexus between the use of these CA-IX specific inhibitors for the diagnosis of cancer. In other words, the specification does not appear to reasonably convey that the inhibitors would specifically recognize CA-IX in tumors, as compared to the tissues expressing other CA isozymes. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of cancer diagnosis is extremely large given the unpredictability associated with the presence of various carbonic anhydrase isozymes (CAIs) being present in both normal as well as cancerous tissues, and the lack of correlation between inhibitor specificity and diagnosis

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that there is a relationship between CA IX expression and a tumor. For example, Zavada et al. (6,027,887, 2000, IDS) teaches that abnormal MN (also referred to as CA IX) expression is a useful diagnostic marker for neoplastic disease because very few normal tissues have been found to express MN protein to any significant degree (column 2, lines 59-61). In particular, Zawada et a. teach that MN protein is overexpressed in a variety of neoplastic disease including, but not limited to, carcinomas of the mammary, prostate, bladder, renal, ovarian, gastrointestinal, uterine and cervical, wherein very few normal tissues have been found to express (column, 3, line 54 to column 4, line 10). Along the same lines, Loncaster et al. (Cancer Research 2001; 61: 6394-6399) discloses that there is a relationship between tumor hypoxia and CA IX expression in human tumors; and that the extent of CA IX expression is a prognostic indicator of a patients outcome (page 6394, 2nd column, 1st full paragraph). In addition to a correlation between CA IX expression and tumor development, the state of the art at the time of filing was such that one of skill could recognize that the CA IX isozyme is not the only carbonic anhydrase expressed in malignant tissue. For example, Parkkila et al. (PNAS 2000; 97: 2220-2224) teach that immunohistochemical studies have indicated that CA II and CA XII are is expressed in renal cancer cell lines (page 2222, Figure 4). In addition to CA II expression in renal cancer cell lines, Parkkila et al. teach that CA II is also highly expressed in several other tumors, including malignant brain tumors and gastic and pancreatic carcinomas (Page 2220, 1st column, 2nd full paragraph). Regarding the brain tumors, Parkkila et al. (Histochemical Journal 1995; 27: 974-982) teaches that immunohistochemical analysis has demonstrated that CA II is highly expressed in brain tumors. Specifically, Parkkila et al. found that the most malignant tumor exhibited the strongest staining (pages 977-979, Figures 1 and 2). Thus, while Parkkila et al. found

high expression levels of CA II in brain tumors, Parkkila et al. teach that since CA II is expressed in various types of neoplastic cells, CA II can not be used as a specific marker for any tumor in neuropathology (page 981, 1st column, 1st full paragraph).

Unlike the references cited above which used immunohistochemical techniques, e.g, antibodies specific for each CA isozyme, for determing CA expression patterns, the instant claims are drawn to method of diagnosis and/ or imaging using CA IX specific inhibitors, wherein the inhibitors encompass aromatic and heterocyclic sulfonamide derivatives. However, those of skill in the art recognize the unpredictability of generating inhibitors specifically for one isozyme of CA. For example, Supuran et al. (Expert Opinion on Therapeutic Patents 2000; 10: 575-600) teach that inhibition of carbonic anhydrases by aromatic/heterocyclic sulfonamides have been exploited in therapy for years. In particular, Supuran et al. teaches that carbonic anhydrase inhibitors have been shown to be useful as diuretics and the treatment an prevention of a variety of diseases such as glaucoma, epilepsy, congestive heart failure, mountain sickness, gastric duodenal ulcers, neurological disorders and osteoporsis, among others (page 576, 2nd column, last paragraph to page 577, 1st column, 1st few lines). However, despite the amount of research that has gone into the construction of CA specific inhibitors, Supuran et al. teach that CA isozymes, such as cytosolic CA I, II and VII, the membrane bound forms CA IV, IX, XII and XIV, or the mitochondrial CA V, show high or very high and similar affinities (in the micro to nanomolar range) for sulphonamide inhibitors which is not a desired situation since inhibition of CAs in sites other than the target organ/tissue may induce undesired side effects of sulphonamide drugs (page 577, 1st column, 6th line from bottom to 2nd column, 5th line). In addition to the development of CA specific inhibitors for the treatment of variety of disorders associated with CA expression, Supuran et al. further contemplates the use of CAIs as diagnostic tools (page 588, 2nd column). In particular, Supuran teaches the possible benefits of using CA inhibitors in both MRI and PET methods for testing cerebrovascular diseases, but cautions that little previous work has been done in this field.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation between CA IX inhibotr specificity and diagnosis of cancer, and the negative teachings in the prior art

balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 67-71, 76 and 78-83 are rejected under 35 U.S.C. 102(b) as anticipated by Zavada et al. (6,027,887, 2000, IDS).

Zavada et al. teach a method of diagnosing/prognosing pre-neoplastic or neoplastic diseases in a mammalian sample, comprising detecting the amount of abnormal MN, e.g., CA IX, protein expression in the sample (column 3, lines 15-54). With regards to detecting, the patent teaches that abnormal MN protein expression can be detected using an antibody which specifically binds to a MN protein (column 7, lines 56+). With regards to the neoplastic disease which can be determined, the patent teaches that the neoplastic disease which can be detected includes, but is not limited to, carcinomas such as mammary, prostate, bladder, renal, ovarian, gastrointestinal, uterine and cervical (column 3, lines 54 to column 4, line 10). In particular, the patent teaches that overexpression of MN is diagnostic for pre-neoplastic/neoplastic disease since most tissues do not express MN protein. In addition to the diagnosis of a neoplastic disease, the patent teaches a method of imaging a tumor comprising administering an antibody appropriately labeled or linked to an imaging agents such as a radionucleotide (column 40, lines 1-14). Thus, Zavada discloses all of the "active steps" of the claimed with the exception of functional limitation that the antibody is a CA-IX specific inhibitor. However, an antibody specific for an MN protein can be reasonably interpreted as a CA IX protein specific inhibitor because the specification defines a CA IX inhibitor as an organic compound. Thus, the claimed compound appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on

the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).
Moreover, while Zavada et al. do not explicitly teach that the method of diagnosis can be used to further provide decision making with respect to hypoxia –selective therapy, the intended use of the method must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art's method is capable of performing the intended use, then it meets the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 77 is rejected under under 35 U.S.C. 103(a) as being obvious over Zavada et al. (6,027,887, 2000, IDS) in view of Sigma® Product Information for Fluoresceine Isothiocynate (12/2000).

Zavada et al. teach, as applied above to claims 67-71, 76 and 78-83 above, a method of diagnosing/prognosing pre-neoplastic or neoplastic diseases in a mammalian sample, comprising detecting the amount of abnormal MN, e.g., CA IX, protein expression is in the sample (column 3, lines 15-54). With regards to detecting, the patent teaches that abnormal MN protein expression can

be detected using an antibody which specifically binds to an MN protein, wherein the antibody is labeled with a fluorescers or dye (column 7, lines 56+ and column 35, lines 31-32).

Zavada et al. do not explicitly teach that the antibody is labeled with fluorescein isothiocynate.

Sigma product information teaches that fluorescein isothiocynate is a commercially available fluorescent label which is widely used for labeling proteins including antibodies.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the antibody as taught by Zavada et al. with a fluorescein isothiocynate label in view of the teachings of Sigma. One would have been motivated to do so because Sigma teaches that fluorescein isothiocynate is a well-known commercially available fluorescent labeling reagent for antibodies. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the antibody as taught by Zavada et al. with a fluorescein isothiocynate label in view of the teachings of Sigma, one would achieve a labeled antibody useful for diagnostic purposes.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 67-68 and 70-84 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-4, 9-10, 12-18 and 31-32 of copending Application No. 11/222,986. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 74-75 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 6-8 of copending Application No. 11/222,986. Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus.

The method of diagnosing a preneoplastic/neoplastic disease associated with abnormal MN/CA IX expression comprising contacting a sample with a specific inhibitor of MN/CA IX, wherein the inhibitor is a compound from 1-92 or an antibody claimed in the conflicting patent application appears to fall with in the same scope of a method of diagnosing a preneoplastic/neoplastic disease associated with abnormal expression of MN/CA IX expression comprising contacting a sample with a specific inhibitor of MN/CA IX claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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